10. Allan CK, Newburger JW, McGrath E, Elder J, Psoinos C, Laussen PC, et al. The relationship between inflammatory activation and clinical outcome after infant cardiopulmonary bypass. *Anesth Analg*. 2010;111:1244-51.
11. Mackie AS, Gauvreau K, Booth KL, Newburger JW, Laussen PC, Roth SJ. Hemodynamic correlates of serum cortisol in neonates after cardiopulmonary bypass. *Pediatr Crit Care Med*. 2011;12:297-303.
12. Wald EL, Preze E, Eickhoff JC, Backer CL. The effect of cardiopulmonary bypass on the hypothalamic-pituitary-adrenal axis in children. *Pediatr Crit Care Med*. 2011;12:190-6.
13. Checchia PA, Backer CL, Bronicki RA, Baden HP, Crawford SE, Green TP, et al. Dexamethasone reduces postoperative troponin levels in children undergoing cardiopulmonary bypass. *Crit Care Med*. 2003;31:1742-5.
14. Pasquali SK, Li JS, He X, Jacobs ML, O'Brien SM, Hall M, et al. Perioperative methylprednisolone and outcome in neonates undergoing heart surgery. *Pediatrics*. 2012;129:e385-91.
15. Pasquali SK, Hall M, Li JS, Peterson ED, Jaggers J, Lodge AJ, et al. Corticosteroids and outcome in children undergoing congenital heart surgery: analysis of the Pediatric Health Information System Database. *Circulation*. 2010;122:2123-30.
16. Carcillo JA, Doughty L, Kofos D, Frye RF, Kaplan SS, Sasser H, et al. Cytochrome p-450 mediated-drug metabolism is reduced in children with sepsis-induced multiple organ failure. *Intensive Care Med*. 2003;29:980-4.
17. Ito S, Kusunoki Y, Oka T, Ito Y, Okuno A, Yoshioka H. Pharmacokinetics of high dose methylprednisolone in children. *Dev Pharmacol Ther*. 1992;19:99-105.
18. Abdel Razzak Z, Loyer P, Fautrel A, Gautier JC, Corcos L, Turlin B, et al. Cytokines down regulate expression of major cytochrome P450 enzymes in adult human hepatocytes in primary culture. *Mol Pharmacol*. 1993;44:707-15.

Discussion

Dr Olaf Reinhartz *(Stanford, Calif)*. Thank you. Dr Crow, you and your group are to be commended for trying to shed light on a subject that still remains quite nebulous to us. The benefits of perioperative steroids for complex congenital repairs are still unclear, and, as of late, as you mentioned, there is even evidence that steroids might actually be harmful at least in some patients. Practice between institutions varies as widely as one would imagine.

Your study is carried out well and has 3 important findings. Number one, blood drug levels despite consistent drug dosage are highly variable, and this variation is not easily explained by patient factors like age, complexity of the procedure, etcetera. Secondly, expectedly and logically higher drug levels lead to more and longer adrenal suppression. And, third, cytokine levels are not different between high and low drug levels in your 2 groups.

I have 2 questions for you. I will ask them one at a time. The first one relates to the large drug level variability. I cannot come up with an explanation why there would be 2 distinct groups as you are describing them, high versus low dexamethasone levels in your study. Did you just arbitrarily categorize these patients into 2 groups? I did not see a scattergram to facilitate analysis. Or, do you really think there are 2 distinct patient populations and you just have not found out yet what distinguishes them?

Dr Crow. Yes, it is an excellent question. We did not have 2 distinct groups. They were scattered around this 15 μg/dL mark that I chose, and I just tried to find a point that looked like most of the group fell above or below in order to make some comparisons.

There is a wide range of variability, but there does appear to be significant differences between the 2 groups. If you divide on that 15 mark, the groups are significantly different between their levels at each point in time.

We do have some studies in methylprednisolone in adults that demonstrate that there is a large variety of components that could contribute to this. And there have even been some studies by Joe Carcillo that show that even in healthy children, we will have differences in drug metabolism.

So inflammatory markers also play into drug metabolism, and IL-6 specifically has been shown to decrease clearance with the cytochrome P450 system, which is utilized to clear dexamethasone.

We did not find a difference in IL-6 levels in our population that would have explained that, but I think it just highlights that there are many, many questions that still need to be investigated to try to figure out why there is such discrepant levels in these patients.

Dr Reinhartz. Secondly, you and others before you have proposed larger prospective multicenter trials around this topic. How would you design these trials? What should the treatment arms be, particularly in light of the more recent data that you mentioned questioning the benefit of perioperative steroids entirely?

Dr Crow. I love this question because I think it is really where the field needs to go now. I think especially with the latest large studies showing potential negative outcomes of corticosteroid treatment. As a result, the clinical equipoise around the practice has grown even in the last 5 years. I am amazed at how much more willing people are to consider not giving corticosteroids intraoperatively. There are now centers that do not give corticosteroids and centers that do give.

So I do think that while we still have some challenges to get people to buy into a randomized clinical trial, which would be the gold standard, there is a possibility to design a study where we take different centers that have different steroid practices, measure these blood levels in those patients in a larger sample, and try to figure out is the best strategy. Are there drug levels that can suppress the components we need to suppress, and will not suppress things like the immune system that are needed to prevent infection?

We have just completed analysis on samples from an additional center, and so we will have the opportunity to look at patients at 2 different centers and have preliminary data to pursue that kind of multicenter investigation. In this scenario, people could still use their standard practices, but we could monitor how those practices translate into postoperative inflammatory/stress responses and try to draw some conclusions from that information.

Dr James S. Tweddell *(Milwaukee, Wis)*. That was a really very interesting study and an excellent presentation. I have just a couple of questions.

How far in advance of skin incision or initiation of bypass were the steroids given?

Dr Crow. Steroids are usually given immediately after the patients are asleep and then right before the bypass prime.

So we had about an hour time period. I actually went and looked at each of them individually, and for all the patients they got 0.5 mg/kg of dexamethasone right after induction and then another 0.5 mg/kg right before bypass was starting. And that was the

standard protocol for all the patients. This time period was about an hour for each patient.

Dr Tweddell. Did you look at any variability in that interval between the first dose and the second dose? Did that have an impact?

Dr Crow. So we actually did not have very much variability. Outside of about 20 minutes, the intervals between those steroids were very similar. You could also question variability in the time between steroid administration and ICU arrival, since we use the level at ICU arrival to divide the patients into 2 groups. There was variability between when bypass started and when it would have finished, and when the patient arrived to the ICU. In an attempt to control for this variability, we compared bypass times between groups. That is sort of a surrogate marker of how long the operative time is for these patients. There were no significant differences in bypass time between groups.

But, again, this is another area where it would be nice to have a larger patient population where you could look a little more discretely at some of those variables. Twenty minutes might end up being significant if you had enough patients to look at it in.

Dr Tweddell. Is there any potential to go back and look at the ACTH levels in these patients?

Dr Crow. Yes. I can actually show it to you right now.

Dr Tweddell. I'm glad I asked a question you are prepared for.

Dr Crow. Well, I did not have time to put it in. Otherwise, I would have shown you that, too.

But the ACTH levels were quite similar to the cortisol levels, and they were similarly suppressed, as you can see, in that high dexamethasone group.

So, it looks like we suppressed the entire axis. And, in fact, dexamethasone is a more potent suppressor of the stress response than your innate cortisol levels. So when I show that negative feedback loop, our cortisol does not suppress the hypothalamus pituitary as much as dexamethasone does.

So, we are really playing with a pretty powerful mediator. And we know the genomic effects of dexamethasone work through transcription and translation and will actually produce a much more prolonged effect on adrenal suppression even after the blood levels have cleared.

So, I think it is very interesting that we have that time period where we are no longer supplementing. Cortisol levels are low and ACTH levels are low, lower even than when the patient first came to surgery.

I am looking forward to looking closer at that 8- and 24-hour time period and beyond to see if we can actually pick out patients that are more labile during that time or kind of seem to be doing okay and then get worse. Is that part of the problem—that we have created this iatrogenic adrenal insufficiency?

Dr Lyle D. Joyce *(Rochester, Minn).* Dr Crow, I assume you would be happy to have any centers here that are interested in joining you to contact you, right?

Dr Crow. Yes. That would be great.

Dr Joyce. Because, as you say, there is variability across the country, and it would be nice to sort that out.

Dr Crow. Yes. The key to answering this question will definitely be multicenter evaluation of what we are already doing.